IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	David J. Grainger et al.	Examiner: Jennifer Kim	
Serial No.:	09/754,775	Group Art Unit: 1617	
Filed:	January 4, 2001	Docket No.: 295.009US3	
Customer No.:	21186	Confirmation No.: 6351	
Title:	PREVENTION AND TREATMENT OF CARDIOVASCULAR PATHOLOGIES WITH TAMOXIFEN ANALOGUES		

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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I, Dr. David J. Grainger, declare and say as follows:

1. I am one of the named co-inventors of the claims of the present application. I make this Declaration in support of the patentability of the claims of the above-identified application.

2. In the Office Action dated February 3, 2009, the Examiner rejected claims 173-175, 177, 179-181, 196-200, 203, 205-206, and 231 under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 (1992)); claims 176, 182, 192, 194, 202, and 205-206 under 35 U.S.C. § 103(a) as being unpatentable over Ito et al. (WO 94/09764); claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 under 35 U.S.C. § 103(a) as being unpatentable over Grainger et al. (WO 94/26303) in view of Chander et al. (Cancer Res., 51:5851 (1991)); claims 173-177, 179-194, 196-199, and 205-206 under 35 U.S.C. § 103(a) as being unpatentable over Yang (U.S. Patent No. 5,445,941); and claims 231 and 234 under 35 U.S.C. § 103(a) as being unpatentable over Yang in view of Frank (Ophthalmology, 98:586 (1991)).

3. Specifically, the Examiner asserts that one of skill in the art would be motivated to use tamoxifen analogs for the expected benefit of lowering total cholesterol (Sawada et al.), treating angitis (Ito et al.), or increasing TGF-beta secretion in order to treat osteoporosis (Yang). The Examiner also asserts that in view of WO 94/26303, there

is a reasonable expectation of successfully treating a disease characterized by a decreased lumen diameter with those analogs.

4. However, prior to the effective filing date of the present application, compounds that were considered to be analogs of tamoxifen were also considered to be anti-estrogens. In particular, prior to the effective filing date of the present application, compounds with structural relatedness to tamoxifen, such as toremifene, were believed to elicit a beneficial effect as a result of their anti-estrogenic activity. As such, it was understood that the target for those compounds was the estrogen receptor (see column 2, lines 39-56 in Yang).

5. For example, Ito et al. disclose the use of nonsteroidal anti-estrogen compounds, such as toremifene, as a remedy for autoimmune diseases (page 1, lines 2-5). Sawada et al. disclose the evaluation of toremifene in mice for the treatment of breast cancer. All treated rodents in Ito et al. and Sawada et al. were female, which implies that toremifene was being used because of its anti-estrogenic property. That conclusion is supported by the generic reference to the class of compounds selected as "non-steroidal anti-estrogens" in the abstract of Ito et al. and the disclosures in both documents. Crucially, there is nothing in either Ito et al. or Sawada et al. that recognizes that certain compounds that are structurally related to tamoxifen have a beneficial effect as a result of their TGF-beta, e.g., TGF-beta1, elevating property, and that this property is unrelated to the anti-estrogenic activity of compounds.

6. Thus, compounds falling within the scope of the generic structure recited in the claims of the present application may have anti-estrogenic properties but all have TGF-beta1 elevating property. It is not therefore possible to infer anything about the likely *in vivo* properties of that class of compounds by learning about specific and unrelated activities of one compound or a sub-class of compounds within that class which have previously been disclosed that happen to share a different property (i.e.,

anti-estrogenic activity) that is not shared by all the members of the class recited in the claims.

7. The Examiner asserts that Yang teaches that toremifene is useful for treating osteoporosis because it induces human fetal fibroblasts to secrete TGF-beta in the absence of the estrogen receptor (citing column 2 and column 4, lines 6-10 in Yang). Nevertheless, the isoform of TGF-beta secreted from those human fetal fibroblasts was not known (column 4, lines 6-9). Moreover, the observation that toremifene induces TGF-beta secretion from human fetal fibroblasts does not logically lead to the conclusion that toremifene is useful for treating osteoporosis because those cells are not present in individuals with osteoporosis.

8. Yang discloses that expression from TGF-beta2 and TGF-beta3 promoters in human osteosarcoma cells transfected with an estrogen receptor encoding construct and exposed to estradiol, raloxifene or tamoxifen, is increased to a much greater extent than expression from TGF-beta1 promoters (see Table I). Thus, any effect observed with estradiol, raloxifene or tamoxifen treatment in Yang most likely is attributed to estrogen receptor binding of those agents.

9. None of Sawada et al., Ito et al. or Yang provides a reasonable expectation that particular compounds that are structurally related to tamoxifen would have an activity that is not associated with the estrogen receptor but is associated with a therapeutic effect *in vivo*. There are a number of examples of such compounds, including raloxifene (see Figure 2 of Yang et al, Endocrinol., 137:2075 (1996)), which has no effect on TGF-beta1 levels *in vivo*, although it has effects on TGF-beta3 consistent with the disclosure in the Yang patent (U.S. Patent No. 5,445,941).

10. Thus, the compounds recited in the claims in the present application form a class united by the elevation of TGF-beta1 activity *in vivo*, which has the recited beneficial therapeutic effects. While that class may overlap with the class of non-steroidal anti-

estrogens, it is not possible to determine the properties of the members of the recited class by understanding the properties of those compounds which also happen to be anti-estrogens and which exert particular properties as a result of that ant-estrogenic activity. The class of compounds recited in the claims of the present application have a set of beneficial properties which do not result from anti-estrogenic activity, and which are attributable to elevated TGF-beta1 activity *in vivo*. In the absence of the present disclosure, there is nothing in the cited documents that would allow one skilled in the art to attribute the particular disclosed beneficial to the particular class of compounds recited in the claims.

11. It was surprising that compounds within the scope of the claims would be useful to inhibit or treat a variety of cardiovascular or vascular indications, since the presence of anti-estrogenic activity in a sub-group of the compounds would not have predicted this. As of the effective filing date of the present application, estrogen was considered to be unequivocally cardioprotective, since (compared to men) women are relatively protected from cardiovascular disease prior to menopause, when estrogen levels are higher, yet after the menopause have a similar age-corrected risk of cardiovascular disease to men. On this basis, anti-estrogens would have been expected, if anything, to exacerbate the risk of cardiovascular disease.

12. The claimed invention is directed to the use of a class of compounds linked by the ability to elevate TGF-beta1 activity *in vivo* and not the sub-class of overlapping compounds with just anti-estrogenic activity. For example, raloxifene (which is anti-estrogenic but does not elevate TGF-beta1) does not prevent cardiovascular disease in humans (Barrett-Connor et al., New England J. Med., 355:125 (2006)), while tamoxifen (which is a less powerful anti-estrogen but does elevate TGF-beta1) does prevent cardiovascular disease in humans (Braithwaite et al., J. Gen. Intern Med., 18:937 (2003)). The extensive literature that supports this conclusion has been reviewed in depth elsewhere (Grainger & Schofield, Circulation, 112:3018 (2005)).

13. The Examiner asserts that in view of the reduction of total cholesterol in female rats after toremifene administration in Sawada et al., one of skill in the art would be motivated to administer toremifene to achieve the expected benefit of lowering total cholesterol in a mammal suffering from atherosclerosis.

14. The lowering of total cholesterol by a particular agent does not by itself have any bearing on whether that the agent would in any way be beneficial in lowering "bad" cholesterol (that is, LDL cholesterol), much less indicate that the agent would be beneficial in preventing or inhibiting heart disease. This is most graphically illustrated by the Women's Health Initiative trial (see Howard et al., J.A.M.A., 295:655 (2006)), in which almost 20,000 women undertook a low fat diet for more than 8 years. Total cholesterol was significantly reduced (as, indeed, was LDL cholesterol) but the incidence of cardiovascular disease was completely unaffected (hazard ratio for heart disease was 0.97 [confidence interval 0.90 – 1.06] and for stroke 1.02 [confidence interval 0.90 – 1.15]). Hence in a larger, well designed and well powered interventional trial, the value of total cholesterol or LDL cholesterol lowering for predicting whether an intervention has benefit on cardiovascular disease was unequivocally shown to be negligible.

15. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 14th July 2009 By David J. Grainger

Dr. David J. Grainger